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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,050	06/29/2007	Kazuya Hosokawa	JCLA21671	3526

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IRVINE, CA 92618

EXAMINER	
TSAY, MARSHA M	
ART UNIT	PAPER NUMBER
1656	
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09/08/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/599,050	HOSOKAWA ET AL.
	Examiner	Art Unit
	Marsha Tsay	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,11-18,20-36 and 38-60* is/are pending in the application.

4a) Of the above claim(s) *5,21-36,40,41,44,49 and 51-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11-18,20,38,39,42,43,45-48,50 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/11; 8/12/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received June 15, 2011.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 6-10, 19, 37 are canceled. Claims 5, 21-36, 40-41, 44, 49, 51-57 are withdrawn. Claims 1-4, 11-18, 20, 38-39, 42-43, 45-48, 50, 58-60, to the species blood coagulation factor 13, are currently under examination.

Priority: The request for priority to JAPAN 2004-080950, filed March 19, 2004, is acknowledged. A certified copy of the foreign priority document has been filed in this case on September 18, 2006, and is in a non-English language.

Objections and Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58-60 are indefinite because it is unclear how the serine at position 205 and histidine at position 43 can correspond to positions 254 and 92, respectively, in SEQ ID NO: 2 since the thrombin derivative already comprises SEQ ID NO: 2.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 11-18, 20, 38, 48, 50, 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07, previously cited) in view of Morrison et al. (2001 Current Opinion in Chemical Biology 5: 304-307; previously cited) in view of current practice in protein design, as evidenced by Wells (1990 Biochemistry 29(37): 8509-8517; previously cited). The Wells reference is cited as a reference to note that it was known in the art at the time of the invention that additive mutagenesis, where a series of single mutants each making a small improvement in function are combined, is a powerful tool in designing functional properties in proteins (Wells p. 8515).

For examination purposes, the instant claims have been interpreted as: a thrombin derivative consisting an A chain and a B chain, wherein the B chain has an amino acid sequence in which serine at position 205 thereof is substituted by alanine, threonine, or glycine, and histidine at position 43 thereof is substituted by alanine or serine. The functional limitations recited in claims 1-2, and their dependent claims are properties that would be present if serine at

position 205 thereof is substituted by alanine, threonine, or glycine, and histidine at position 43 thereof is substituted by alanine or serine.

Arcone et al. disclose human thrombin mutants where single amino acid substitutions were introduced in the catalytic triad (H43N, D99N, S205A, S205T) (p. 173). Arcone et al. further disclose that mutations S205A and G203A completely abolished the enzyme activity and that mutations H43N, D99N, and S205T dramatically impaired the enzyme activity toward a chromogenic substrate and fibrinogen (p. 173, p. 179, also Table I). Arcone et al. do not explicitly teach the combination of S205 substituted with alanine, threonine, or glycine in combination with H43 substituted with alanine or serine.

Morrison et al. disclose that combinatorial alanine-scanning can be used to rapidly identify residues important for protein function, stability and shape (p. 302). Morrison et al. further disclose replacement amino acid residues that can be used to substitute for the wild-type amino acid (p. 303). As noted in table 1, Morrison et al. disclose that a wild-type serine residue can be replaced with Ala/Ser and a wild-type histidine residue can be replaced with Ala/His/Asp/Pro (p. 303).

Further, as evidenced by Wells, it is known that single amino acid substitutions can be combined so that their effects on a protein are cumulative (p. 8515).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Arcone et al. by combining the single amino acid substitutions of Arcone et al., S205 and H43, in which S205 is substituted with alanine and H43 is substituted with alanine, in view of what is known in the art about protein design (as disclosed by Morrison et al. and Wells) in order to make a modified thrombin protein that has decreased or

no enzymatic activity (claims 1-4, 11-18, 20, 38, 48, 50, 58-60). The motivation to do so is given by Arcone et al. in view of Morrison et al. and Wells, which disclose that single amino acid substitutions at the catalytic triad disrupts the enzymatic activity of thrombin; therefore, it would be reasonable for one of ordinary skill to combine the single amino acid substitutions selected from H43, D99, and S205, in order to arrive at the combination of H43 and S205 because there are only three residues at the catalytic triad and it would be reasonable to determine which two residues, when substituted in combination, will make a modified thrombin protein that has approximately no enzymatic activity, using the technology of Morrison et al. and Wells.

Regarding the additional amino acids, besides alanine, that S205 and H43 can be substituted with, it should be noted that table I discloses replacement amino acids that include threonine, glycine, and serine; therefore, it would be reasonable for one of ordinary skill to know that wild-type serine and histidine could also be replaced with threonine, glycine, and/or serine since the other amino acids having the same properties as serine and histidine can be replaced with the amino acids threonine, glycine, and/or serine.

Regarding the functional limitations recited in claims 1-4, 13-18, 48, said limitations are properties that would be present since at the time of the invention, it would be reasonable for one of ordinary skill to arrive at the combination of the substitutions S205A and H43A, as disclosed by Arcone et al. in view of Morrison et al. and Wells.

Arcone et al. disclose human thrombin mutants; therefore, it would be reasonable for one of ordinary skill to know that the thrombin B chain of Arcone et al. is an amino acid sequence of a B chain of human wild-type thrombin (claim 38, 58-60).

Arcone et al. disclose a liquid composition of the purified thrombin mutants; therefore, it would have been obvious to one of ordinary skill to know that said modified thrombin protein of Arcone et al. as evidenced by Wells can also be incorporated into a liquid composition (claim 50).

In their remarks, Applicants assert that **(1)** the thrombin derivative of each independent claim 1, 2 or 20 features the mutations at serine at position 205 (S205), and histidine at position 43 (H43). Arcone et al. disclose the thrombin mutants each having a single mutation such as S205T, D99N, H43N, S205A or G203A, but disclose no thrombin mutant having a double mutation at both H43 and S205. The single mutants disclosed in Arcone et al. still have thrombin activity, and therefore cannot be used as antithrombotic agent. Though Arcone et al. describe in Abstract *"Mutations S205A and G203A completely abolished the enzymatic activity"*, the activity was evaluated by the assay using synthetic peptide S-2238 as a substrate (see section 2.5 of Arcone et al.). In the assay, the residual activity of the thrombin mutants cannot be detected. In fact, this application shows that G203A still has thrombin activity detectable by the assay using FXIII and fibrinogen as a substrate (Experimental Example 15 and Fig. 20). S205T also has thrombin activity detectable by the assay using FXIII as substrate (Experimental Example 4). Such mutant thrombins maintaining some thrombin activity cannot be used as an antithrombotic agent because of the side effects caused by the residual proteolytic activity of the mutants. **(2)** Moreover, single mutants disclosed in Arcone et al. have decreased binding ability to substrates such as FVIII and thrombin receptor. For example, Experimental Example 3 showed that the FVIII binding signal of S205A mutant decreased to about 40% as compared to

that of AHT (anhydrothrombin). The binding ability is indispensable property for exerting the antithrombotic activity. As described in Experimental Example 3 (paragraph [0123]), the S205A thrombin mutant does not have the thrombin receptor-activating ability of a level at which the S205A mutant can be practically used as an antiplatelet agent in plasma. The decreased binding of the S205A mutant to the substrates such as FVIII and thrombin receptor resulted in weak APTT-prolonging effect ([0123]). Other mutants also have decreased binding ability to the substrates (S205V (Example 6), S205D (Example 7), S205N (Example 8), and S205G (Example 24)), and cannot be used as an antithrombotic agent. On the other hand, the thrombin mutants having mutations at S205 and H43 have completely lost the thrombin activity but maintained the substrate binding ability (more than that of AHT) as described in paragraphs [0145], [0152], [0172] and [0173] of this application, thereby exerting a significant APTT-prolonging effect and an antiplatelet effect to be suitably used as an antithrombotic agent. Such effects cannot be obtained by randomly combining the single mutations taught by Arcone et al. according to the current practice in protein design (Wells). For example, G203A, S205G D99N, S205A D99N, G203A S205A and G203A S205G in Experimental Examples 5, 10, 11 and 2 respectively have decreased binding ability to the substrates and little APTT-prolonging effect. Further, these mutants cannot exert the antiplatelet effect. **(3)** Moreover, Morrison et al. simply teach a general method of studying the importance of a non-alanine amino acid by substituting the amino acid with alanine (see Abstract), and either cannot show an effect of combining the mutations at S205 and H43. For at least the above reasons, one of ordinary skill in the art could have never been expected from the teachings of Arcone et al., Morrison et al., and current practice in protein design (Wells) that an excellent antithrombotic agent having a significant APTT-prolonging

effect and an antiplatelet effect can be obtained by combining the mutations at S205 and H43. The other references cited for rejecting some dependent claims, Veronese and Roberts et al., also fail to teach the above feature of the independent claims. For at least the above reasons, amended claims 1-2 & 20 and claims 3-4, 11-18, 38-39, 42-43, 45-48, 50 & 58-60 dependent therefrom all patently define over the prior art.

Applicant's arguments have been fully considered but they are not persuasive.

(1) **Reply**: Applicants are reminded that "the references cannot be used in isolation, but for what they reach in combination with the prior art as a whole. *In re Merck,* 800 F.2d 1091, 1097 (Fed. Cir. 1986).

At the time that the invention was made, it was known in the art that combinatorial alanine-scanning can be used to rapidly identify residues important for protein function, stability and shape (Morrison et al.) and that single amino acid substitutions can be combined so that their effects on a protein are cumulative (Wells et al.). Arcone et al. disclose a finite number of amino acid substitutions in the catalytic triad of thrombin (i.e. (H43N, D99N, S205A, S205T), where single amino acid substitutions disrupted the enzyme activity. It should be noted that a claimed compound would have been obvious where it was obvious to try to obtain it from a finite and easily traversed number of options that was narrowed down from a larger set of possibilities by the prior art, and the outcome of obtaining the claimed compound was reasonably predicted. Bayer Schering Pharma A.G.v. Barr Labs., Inc., 575 F.3d 1341 (Fed. Cir. 2009). Therefore, it would have been reasonable for one of ordinary skill to arrive at a modified thrombin protein that has the double mutations S205A and H43A because there are only a finite number of amino acid substitutions to choose from in the catalytic triad.

Regarding Applicants' remarks on the assays used in Arcone et al. to detect the activity of the thrombin mutants, it should be noted that mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). One of ordinary skill can still reasonably arrive at the instant combination of amino acid substitutions in a thrombin mutant regardless of the assays used to test the enzymatic activity of said thrombin mutant.

(2) Reply: It should be noted that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 441 F.3d 977,987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

In this instance, Arcone et al. disclose a finite number of amino acid substitutions in the catalytic triad of thrombin (i.e. (H43N, D99N, S205A, S205T), where single amino acid substitutions disrupted the enzyme activity. At the time that the invention was made, it was known in the art that combinatorial alanine-scanning can be used to rapidly identify residues important for protein function, stability and shape (Morrison et al.) and that single amino acid substitutions can be combined so that their effects on a protein are cumulative (Wells et al.). Since each single amino acid substitution in the catalytic triad was identified to disrupt enzyme activity, it would be reasonable for one of ordinary skill to combine the single amino acid substitutions selected from H43, D99, and S205, in order to arrive at the combination of H43 and S205 because there are only three residues at the catalytic triad and it would be reasonable to determine which two residues, when substituted in combination, will make a modified thrombin

protein that has approximately no enzymatic activity, using the technology of Morrison et al. and Wells.

(3) Reply: The Morrison et al. reference was cited to note that at the time of the invention, combinatorial alanine-scanning technology can be used to rapidly identify residues important for protein function, stability and shape.

MPEP 2143 states that that the rationale to support a conclusion that the claim would have been obvious is that a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product and the results would have been predictable to one of ordinary skill in the art.

The deficiency of Morrison et al. to show an effect of combining the mutations at S205 and H43 is believed to be remedied by the Wells et al. reference.

See also the replies of (1) and (2).

For at least these reasons, the claims remain rejected under 35 U.S.C. 103(a).

Claims 39, 42-43, 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07, previously cited) in view of Morrison et al. (2001 Current Opinion in Chemical Biology 5: 304-307; previously cited) in view of current practice in protein design, as evidenced by Wells (1990 Biochemistry 29(37): 8509-8517; previously cited) in view of Veronese (2001 Biomaterials 22: 405-417; previously cited). The teachings of Arcone et al. in view of Morrison et al. in view of

Wells are outlined above. Arcone et al. in view of Morrison et al. in view of Wells do not teach modifying a carboxyl group with polyethylene glycol (PEG).

Veronese et al. disclose that PEGylation of proteins enhances the therapeutic and biotechnological potential of proteins (p. 405). When PEG is properly linked to a protein, it modifies many of the protein's features while maintaining its biological functions, i.e. PEG increases the molecular size of the protein and can also reduce its degradation by proteolytic enzymes (p. 406). Veronese discloses general PEGylation chemistry to show that arginine residues and carboxyl groups on a protein can be modified, i.e. PEGylated (p. 410).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the amino acid substituted thrombin mutant of Arcone et al. in view of Morrison et al. in view of Wells by modifying the carboxyl groups of said thrombin mutant with PEG, as suggested by Veronese et al. (claims 39, 42-43, 45-46). The motivation to do so is given by Veronese et al., which disclose that PEG can be linked to a protein, i.e. arginine residues or carboxyl groups, to enhance its therapeutic and biotechnological potential.

Regarding the limitations of claims 43, 45-46, it would be reasonable for one of ordinary skill to want to determine the optimum molecular weight of the PEG and the number of carboxyl groups to be PEGylated in order to make a modified thrombin protein with the level of therapeutic and biotechnological potential that one of ordinary skill would like.

Reply: The reasons for maintaining the 35 U.S.C. 103(a) rejection are the same as noted above.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07, previously cited) in view of Morrison et al. (2001 Current Opinion in Chemical Biology 5: 304-307) in view of current practice in protein design, as evidenced by Wells (1990 Biochemistry 29(37): 8509-8517; previously cited) in view of Veronese (2001 Biomaterials 22: 405-417; previously cited) in view of Roberts et al. (2002 Advanced Drug Delivery Reviews 54: 459-476; previously cited). The teachings of Arcone et al. in view of Morrison et al. in view of Wells et al. in view of Veronese are outlined above. Arcone et al. in view of Morrison et al. in view of Wells et al. in view of Veronese do not teach PEGylating a carboxyl group of a glutamic acid at position 25 in the B chain.

Roberts et al. disclose that glutamic acid is a typical reactive amino acid that can be PEGylated (p. 461).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the amino acid substituted thrombin mutant of Arcone et al. in view of Morrison et al. in view of Wells et al. in view of Veronese by PEGylating a carboxyl group of a glutamic acid residue in said thrombin mutant, as suggested by Roberts et al. (claim 47). The motivation to do so is given by Roberts et al., which disclose that a typical reactive amino acid in PEGylation chemistry is glutamic acid; therefore, it would be reasonable for one of ordinary skill to determine which residues on said thrombin mutant is best suited for PEGylation, i.e. glutamic acid residues on the B chain, including the one at position 25.

Reply: The reasons for maintaining the 35 U.S.C. 103(a) rejection are the same as noted above.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marsha Tsay/
Patent Examiner, Art Unit 1656

August 29, 2011